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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/493,211	01/28/00	APPELMELK B	Q57666

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1653	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/493,211	Applicant(s) APPELMELK ET AL.	
	Examiner Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *14 and 31-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,13 and 15-30* is/are rejected.

7)☒ Claim(s) *8-12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-7, 11 (SEQ ID NO:4), 13 and 15-30 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the search and examination of the entire application can be made without serious burden, and it should be examined based on the merits, even though it includes distinct or independent inventions. This is not found persuasive because the traversal is not on the grounds that the inventions are not independent and distinct, rather, the traversal is on the grounds that the burden of search is not undue. As such restriction is proper if two or more claimed inventions are either independent **or** distinct. See MPEP 803. Furthermore, coexamination of each of the additional groups would require search of classes unnecessary for the examination of the elected claims (Group I). For example, if Group II were included, it would require additional search of class 435, subclass 69.7. Therefore, coexamination of each of these inventions would require a serious additional burden of search.

The restriction groups have acquired a separate status in the art as a separate subject for inventive effect and require independent searches. The search for each of the invention is not coextensive particularly with regard to the literature search. A reference which would anticipate the invention of one group would not necessarily anticipate or make obvious any of the other group. Moreover, as to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the

burden of search. Burden in examining materially different groups having materially different issues also exist.

The Examiner recognizes BP1 (SEQ ID NO:1), BP2 (SEQ ID NO:2), BP2.3 (SEQ ID NO:3), BP2.4 (SEQ ID NO:4) and BP2.5 (SEQ ID NO:5) have the core sequence of the formula of claim 1, thus withdraws the species election of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objection

1. Claims 8-12 are objected to because of the use of the term "SEQ ID NO." The term "SEQ ID NO:" instead of "SEQ ID NO." should be used. See 37 CFR 1.821(d).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a peptide (claim 1). As written, the claim does not explicitly indicate the hand of man. Insertion of "purified" in connection with a peptide is suggested. See MPEP § 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-7, 13 and 15-30 are rejected under 35 U.S.C. 112, first paragraph.

Claims 1-7, 13 and 15-30 are rejected because the specification, while being enabling for 8 peptides (BP1, BP2, BP2.3, BP2.4, BP2.5, BP1.1, BP2.1 and BP2.2) which comprise at least 12 amino acids and are amphipathic, cationic and form stable α-helix, does not reasonably provide enablement for peptides of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) which comprise at least 12 amino acids and are amphipathic, cationic and form stable α-helix. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-7, 13 and 15-30 are drawn to peptides of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) or pharmaceutical compositions comprising the peptides, or a method of treatment of a mammal suffering from microbial infection comprising administering a peptide of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3). The specification, however, only discloses cursory conclusions (page 10, lines 15-page 11, line 16), without data to support the findings, which state that peptides of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) or pharmaceutical compositions comprising the peptides which comprise at least 12 amino acids and are amphipathic, cationic and form stable α-helix. There is no disclosure or description of any data indicating peptides of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) have α-helix structures, e.g., data from circular dichroism, Fourier Transform infrared or x-ray crystal structure. It is known that secondary structures such as α-helix, β-sheet or random coil of protein or peptides can be predicted using the scheme of Chow and Fasman with the secondary structure conformation parameters of amino acid residues in the sequence (see Cantor et al., Biophysical Chemistry Part I: The Conformation of Biological Macromolecules, pages 298-305 (1980)). For example, the analysis of BP1, BP2, BP2.3, BP2.4, BP2.5, BP1.1, BP2.1 and BP2.2 using α-helix and β-sheet conformation

parameters indicating these peptides would have α-helix structures, while a peptide of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) such as Gly-Arg-Tyr-Arg-Ile-Tyr-Arg-Arg-Ile-Tyr-Arg-Arg-Tyr-Ile-Arg-Ile-Ile-Ile-Gly would have β-sheet structure rather than α-helix. Therefore, actual measurements of the α-helix or β-sheet structures of peptides using various methods are necessary in order to confirm the predicted secondary structures let alone antimicrobial function (See below). Despite knowledge in the art for α-helix structures of peptides, the claims encompass enormous numbers of peptides which would not be expected by the skilled artisan to accomplish the method set forth. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such peptides in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Claims 15-27 are drawn to a pharmaceutical composition comprising a peptide of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) for treating microbial or parasite infections, topic and systemic tumors, inflammation, septic shock or the treatment being prophylactic. The specification, however, only discloses cursory conclusions (page 5, lines 25 – page 6, lines 11; page 22, lines 3-12, 22-23), without data to support the findings, which state a pharmaceutical composition comprising a peptide of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) for treating infection caused by a bacterium, a fungus, a virus or a parasite, or treating topic and systemic tumors, inflammation or septic shock, or the treatment being prophylactic. The specification only discloses peptides such as BP1, BP2, BP2.1 or BP 2.2 have antibacterial activity against gram-positive or gram-negative bacteria (pages 14-23 and Table 1). There is no disclosure or

description of data regarding pharmaceutical compositions comprising other peptides of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) than BP1, BP2, BP2.1 and BP 2.2 for treating microbial infections. The specification has not demonstrated a pharmaceutical composition comprising any peptide of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) being used for treating fungus, virus or parasite infection, or treating topic and systemic tumors, inflammation or septic shock, or the treatment being prophylactic. Despite knowledge in the art for amphiphilic peptides with antimicrobial properties, the claims encompass enormous numbers of peptides or various disease states which would not be expected by the skilled artisan to accomplish the method set forth. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such peptides in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Claims 28-30 are drawn to a method of treatment of a mammal including human suffering from microbial infection comprising administering a peptide of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3). The specification, however, only discloses the administration of BP 2 in mice has increased the survival rates in murine models (page 20, line 23-page 21, line 22). There is no data demonstrated the treatment of microbial infection using the peptide of formula (R^1-R^2-A-B-(A-B-C-A)$_m$-(C)$_n$-R^3) being effective in humans. Since it is not routine in the art to engage in *de novo* experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to make and use such peptides in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue. See for example, Table 1 of the

specification does not demonstrate how to predict the expected effects of other peptides defined in the application formula claimed. Note the disparate activity with regard to different bacteria shown in Table 1, while one may conclude BP1 and BP2 are effective, what would have been the expected results for other peptides such as BP2.3 (SEQ ID NO:3), BP2.4 (SEQ ID NO:4) and BP2.5 (SEQ ID NO:5)?

The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the scope of the claims, the nature of the invention, the working examples, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary as discussed in the preceding paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 6-7, 13 and 15-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for because of the use of the term "R^1-R^2 and R^3 are a number of amino acids" or "wherein one or more of the repetitive sequence motifs (A-B-C-A)". The term "R^1-R^2 and R^3 are a number of amino acids" or "wherein one or more of the repetitive sequence motifs (A-B-C-A)" renders the claim indefinite, it is unclear in the claim what kind of peptide is intended, e.g., how many amino acids and what kind of amino acids are for R^1-R^2 and R^3, or how many repetitive sequence motifs (A-B-C-A) are in the formula. Claims 6-7, 13 and 15-30 are included in the rejection for being dependent of a rejected claim and not correcting the deficiency of the claim from which they depend.

5. Claim 2 is indefinite for because of the use of the term "R^1-R^2 and R^3 each have a number of amino acids ranging from 0 to 15". The term "R^1-R^2 and R^3 each have a number of amino acids ranging from 0 to 15" renders the claim indefinite, it is unclear in the claim what kind of peptide is, e.g., how many amino acids and what kind of amino acids are for R^1-R^2 and R^3. The same rejection is also applied to claim 3.

6. Claim 5 is indefinite because of the use of the term "and/or". The term "and/or" renders the claim indefinite, it is unclear in the claim whether R^3 comprises an amino acid from those of group A, B or C. The same rejection is also applied to claims 15 and 21.

7. Claim 6 is indefinite because of the use of the term "more often than". The term "more often than" renders the claim indefinite, it is unclear in the claim how often (A-C-B-A) is more than (A-B-C-A) in the formula.

8. Claim 13 is indefinite for because of the use of the term "a non-peptide carrier, tag or label". The term "a non-peptide carrier, tag or label" renders the claim indefinite, it is unclear in the claim what kind of carrier, tag or label the peptide is coupled to.

9. Claim 21 is indefinite for because of the use of the term "a mixture of at least two peptides according to claim 1". The term "a mixture of at least two peptides according to claim 1" renders the claim indefinite, it is unclear in the claim how many peptides and how much of each peptide are included in the mixture.

10. Claim 22 is indefinite because of the use of the term "derivatives or analogues". The term "derivatives or analogues" renders the claim indefinite, it is unclear what kind of antibiotics are intended as compared to the parent compounds.

11. Claim 22 is indefinite because of the use of the term "has or can have occurred". The term "has or can have occurred" renders the claim indefinite, it is unclear whether the trauma or suspected infection has occurred or not.

12. Regarding claim 23, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

13. Claims 28-30 are indefinite because they lack essential steps as claimed in the process of treating mammal suffering from microbial infection. The omitted steps are: the site and method of administration, the therapeutically effective amount of peptides and a step whereby the desired outcome and the length of the treatment using the peptide can be determined.

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

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July 7, 2001

Christopher S. F. Low
CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.